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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,889	12/15/2003	Elias Georges	112418-147 and AUR-013US	5738

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
04/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/736,889	GEORGES ET AL.	
	Examiner	Art Unit	
	LEI YAO	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-108* is/are pending in the application.

4a) Of the above claim(s) *11,13,20-58,67,69 and 75-108* is/are withdrawn from consideration.

5)☐ Claim(s) *1-9,59-65* is/are allowed.

6)☒ Claim(s) *10,12,14-19,66,68 and 70-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Arguments

The Amendment filed on 2/13/2008 in response to the previous Non-Final Office Action (8/13/2007) is acknowledged and has been entered.

Claims 1-108 are pending.

Claims 11, 13, 20-58, 67, 69, 75-108 have been withdrawn previously.

Claims 1-9 and 59-65 have been allowed.

Claims 10, 12, 14-19, 66, 68 and 70-74 are under consideration.

Declaration

Declaration by Elias Georges submitted on 2/13/2008 has been considered (see below).

Response to Arguments and Declaration

35 U.S.C. 112 1st paragraph-Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 12, 14-19, 66, 68 and 70-74 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as stated the following:

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of necessary experimentation claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir.1988).

The claims are drawn to an in vivo method of detecting a multidrug resistant (MDR) or neoplastic cell in a patient comprising administering to a patient in a vimentin binding agent comprising modified LDL linked to detectable agents comprising fluorophores, wherein the binding agent specifically binds to cell surface-expressed vimentin presented on a multidrug resistant cell or neoplastic cell in patients. The specification teaches that tissue cultured MDR cells or neoplastic cells express vimentin on the surface of the cells and teaches that the ligands for vimentin comprise modified LDL (example 5-9, page 103-108). The specification contemplates a method for detecting a MDR cancer cells or neoplastic cells comprising administering detectable linked modified LDL or other vimentin ligands (paragraph 33), but no result or example has been provided. The specification does not provide any guideline/direction or teaching on the correlation of in vivo detecting of any patient having MDR or neoplastic cells with the in vitro assay of expression of vimentin on the surface of those cells. Therefore, one skilled in the art would not know how to use the claimed method to diagnose or detect MDR cells or neoplastic cells in a patient based on the teachings in instant specification or the prior art.

With regards to the correlation between in vitro and in vivo, the state of the art recognizes that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are unpredictable and generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in- vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost (p. 4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994, vol12, page 320) teaches that, petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer states that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

In addition, one skilled in the art has recognized the barriers of tumor imaging for the diagnosing and detection. Kuszyk et al., (American Roentgen Ray, vol 177:745-753, 2001) states “the types of barriers to molecular delivery of drugs may be categorized by the boundaries that the molecule encounters as it travels from the bloodstream to the targeted tumor cell—barriers to the bloodborne delivery to the solid tumor, barriers to crossing the vessel wall, and barriers to crossing the interstitium to the targeted tumor cell. Some of these barriers are related: increased interstitial pressure in tumors hinders both transport across the vessel wall and transport across the interstitium. Nevertheless, this classification provides a framework for thinking about these problems” (page 749, bridge col 1-2).

Because of the problems encountered in the art and the nature of unpredictability of claimed invention, the in vivo experimentation demonstrating that the MDR cells or neoplastic cells are detectable by modified LDL binding to surface expressed vimentin is necessary before one skilled in the art use and practice claimed invention. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to the claimed method, one skilled in the art would be forced into under go an undue quantity of experimentations in order to practice claimed invention in patients.

The declaration by Elisa Georges and the response based on the declaration in the remarks filed 2/13/2008 have been carefully considered but are not to be persuasive and the declaration is insufficient to overcome the rejection. The reasons are the following:

The claims are drawn to a in vivo method for detecting a multidrug resistant (MDR) or neoplastic cell in a patient comprising administering to the patient a vimentin biding agent that is modified LDL (elected).

The declaration provides:

In vitro expression of vimentin on the breast cancer cells (figure 1 and paragraph 13).

In vivo treating tumor bearing mice with taxol + ^{131}I labeled vimentin antibody in combination (figure 2-4 and paragraph 9-12). It is noted that the antibody and taxol are not conjugated.

Based on the result, applicant on page 4 of the remark states:

> The data indicates that the anti-vimentin antibodies bound to cell-surface- expressed vimentin, thereby enhancing the effects of taxol on the cancer cells (line 5).
> and
> The data proves that ^{131}I labeled anti-vimentin antibodies bind to cell-surface-expressed vimentin in vivo (see Georges Dec. 77 10-13). This is apparent because in vitro data from cells transiently expressing increased levels of vimentin shows that tumor cells express increasing levels of vimentin on the cell surface. The monoclonal antibody used in the in vivo experiments binds specifically to vimentin, and only bind to cell-surface-expressed vimentin in these experiments because antibodies, due to their size, do not cross the cell membrane into the cytosol with any appreciable efficiency (paragraph 2).

In response, first, applicant has originally elected modified LDL as a species of vimentin binding agents for examining claimed invention drawn to a method of detecting MDR cell or neoplastic cells. Using anti-vimentin for treating a cancer cells is neither an elected invention, nor an elected species for elected invention as claimed. Second, the declaration although provides a result of treating tumor-bearing mice by anti-vimentin plus taxol, it does not overcome the rejection under USC 112- enablement for claimed invention drawn to a method of detecting a MDR or neoplastic cell comprising administering the patient a modified LDL that specifically binds to the surface expressed vimentin. The instant specification actually has provided contradictory teaching on the antibody binding to the surface of the cells as the argument above, "*antibodies, due to their size, do not cross the cell membrane into the cytosol*". The specification, figure 19 and example 17 (page 115, line 28+) teaches that the ^{125}I labeled anti-vimentin antibody is actively taken up by endocytosis. This observation would suggest one skilled in the art that the antibody or the method may not be good or enabled for detecting the neoplastic cell because the antibody and antigen is actively internalized by the cells. Therefore, administering the antibody to vimentin may not give a direction or guideline or any prediction of using any other vimentin binding agent especially modified LDL for detecting the MDR or neoplastic cells that express vimentin on the surface.

Regarding to the elected species, modified LDL, as vimentin binding agent, declaration (paragraph 14, 16) and response on page 5 of the remarks states:

modified LDL is a known binding agent of vimentin, and binds to vimentin with high specificity (see Specification, paragraph [0194], citing, Heidenthal, et al. (2000) Biochem. Biophys. Res. Comm. 267: 49-53). With this knowledge and the teachings of the specification, one of ordinary skill in the art could utilize modified LDL as vimentin targeting agent. Furthermore, the data provided herewith shows that vimentin targeting agents would bind in vivo to cell-surface-expressed vimentin. Therefore, those of ordinary skill in the art are enabled to practice the full scope of the claimed invention, including in vivo detection using vimentin targeting agents, without undue experimentation.

In response, first Heidenthal, et al. disclose that intracellular vimentin (the filaments extend through the cytoplasm as far as inner face of plasma) binds to the AcLDL (modified LDL) assayed by cell free system (membrane isolated from macrophage), which provides no teaching on the binding AcLDL on the surface expressed vimentin, therefore no evidence the AcLDL or other modified LDL could be used for detecting the cells having the surface expression of vimentin. In addition, more important, Fanger et al., (US Patent 5762930, provided in the Office action, 9/21/2005) teach that AcLDL binds to Fc gamma receptor on the macrophages or monocytes in vivo (col 13-15), which would suggest that the binding vimentin by AcLDL is not specific for the neoplastic cells or multiple drug resistant cells which could not be used for detecting the MDR or neoplastic cells having vimentin on the surface.

Thus, Applicant's argument has not been found persuasive, and the rejection is maintained.

Conclusion

Claims 1-9 and 59-65 have been allowed. Claims 10, 12, 14-19, 66, 68 and 70-74 are rejected.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643